Regioselective Synthesis of Mixed Indole 2,3-Bis(sulfides). A Study of the Mechanism of the Second Sulfenylation of Indole

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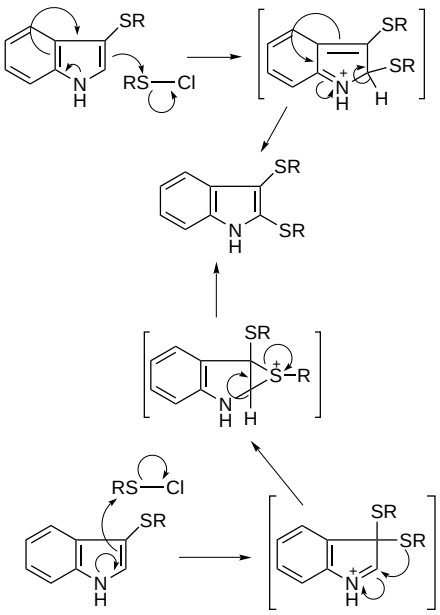
Sulfenylation of indole using sulfenyl chlorides leads to the initial formation of a 3-indolyl sulfide, while excess reagent introduces a second sulfide at the 2-position of the ring. The mechanism of this second sulfenylation has not, to date, been rigorously elucidated. The development of the first, regioselective synthesis of mixed indole 2,3-bis(sulfides) has allowed the study of the sulfenylation of 3-indolyl sulfides using a different sulfenyl chloride. Our results afford evidence that the reaction proceeds via an intermediate 3,3-disulfenylated indolenine species, with subsequent migration of one of the sulfide groups to the 2-position.

Introduction of a sulfide group at the 3-position of indole can be accomplished in several ways. For instance, indole can react with KI_3, followed by thiourea, with subsequent basic hydrolysis to generate *in situ* the 3-indolyl thiolate which may be alkylated.[1] Alternatively, 3-indolyl sulfides may be obtained by sulfenylation, either by reaction of indole anion with a disulfide[2] or by the action of a sulfenyl chloride on indole itself,[3] this last procedure being applicable also to N-substituted indoles. The first two methods lead to exclusive introduction of the sulfide into the 3-position, and no further sulfenylation occurs in the presence of excess reagents. However, when sulfenyl chlorides are used, if the 2-position is unsubstituted, excess reagent leads to a facile second sulfenylation, affording indole 2,3-bis(sulfides).

The mechanism for the introduction of the second sulfide group has, to date, not been rigorously elucidated. Although it is possible to draw a mechanism which leads to direct substitution at the 2-position (eq 1), a more plausible pathway was proposed by Ottenheijm[4] (eq 2), where the second sulfenylation initially occurs at the 3-position, affording an intermediate 3,3-indolenine bis(sulfide). Since the presence of a sulfide at the 3-position of the indole would not be expected to deactivate that position, it is reasonable, barring steric factors, to propose a second attack at that most nucleophilic position. Migration of one of the sulfides to the 2-position promoted by the positive charge on the indolenium cation is proposed to occur via an episulfonium species.

In a very extensive and elegant series of experiments, A. H. Jackson and co-workers[5] provided convincing evidence that alkylation of Grignard derivatives of 3-alkylindoles occurs by initial formation of 3,3-disubstituted indolenines, followed by rearrangement to 2,3-dialkylindoles, and that this migration occurs in an intramolecular fashion. In this paper, we supply evidence that the sulfenylation of 3-indolyl sulfides also occurs predominantly, possibly completely, via a similar initial substitution at the 3-position, with subsequent migration.



Materials and Methods

In the process outlined in eq 2, the second sulfenylation leads to a 3,3-bis(sulfide) in which the two groups are identical so that migration of either one leads to the same 2,3-bis(sulfide). One apparently simple and obvious way to resolve the mechanistic dilemma of direct vs indirect introduction of the sulfide group into the 2-position would be to perform the second sulfenylation of a 3-indolyl sulfide using a different sulfenyl chloride. Thus, if direct substitution were to occur as in eq 1, the second sulfide should be introduced at the 2-position, resulting in a single mixed bis(sulfide), whereas initial reaction at the 3-position would most likely lead to a mixture of two mixed bis(sulfides), the composition of which would be dictated by the relative propensities for migration of the two sulfide moieties. This apparently simple concept suffered from a major drawback: although we were confident that the two isomers could be separated and quantified, there remained the problem of structural assignment, since there exist no examples of mixed indole 2,3-bis(sulfides) in the chemical literature to date.

The ideal solution was to develop a method to obtain authentic samples of these mixed bis(sulfides) through selective synthesis which would allow unambiguous assignment of the positions of the two sulfide groups.

† Mr. Patrice Préville performed part of this work during a student work term.

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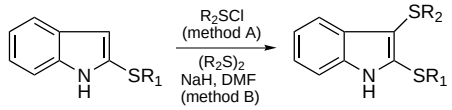
(2) Atkinson, J. G.; Hamel, P.; Girard, Y. *Synthesis* **1988**, 480.
(3) Anzai, K. *J. Heterocycl. Chem.* **1979**, *16*, 567.
(4) Plate, R.; Nivard, R. J. F.; Ottenheijm, H. C. J. *Tetrahedron* **1986**, *42*, 4503.
(5) Biswas, K. M.; Jackson, A. H. *Tetrahedron* **1969**, *25*, 227 and references therein.

0022-3263/96/1961-1573$12.00/0

Table 1. Regioselective Synthesis of Mixed Indole 2,3-Bis(sulfides)



1 **2**

example	method	R_1	R_2	yield of **2** (%)
a	A	CH_3	Ph	89
b	A	Ph	CH_3	80
c	A	Ph	4-MeOPh	73
d	A	4-MeOPh	Ph	82
e	A	4-MeOPh	4-NO_2Ph	84
f	A	4-NO_2Ph	4-MeOPh	80
g	B	4-ClPh	4-MeOPh	81
h	B	4-MeOPh	4-ClPh	88

These compounds could then be used as standards for the quantitation of the reaction mixtures by analytical techniques, preferably HPLC, without the need to perform tedious separation of the isomers.

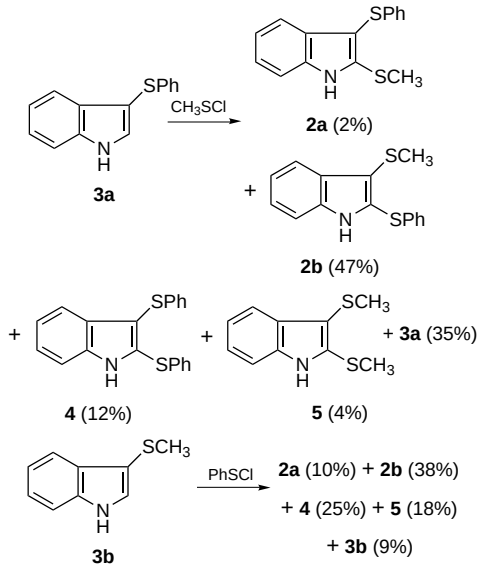
The first regiospecific preparation of the mixed indole 2,3-bis(sulfides) was made possible by two recent syntheses of 2-indolyl sulfides: acid-catalyzed isomerization of 3-indolyl sulfides[6,7] and our recent method for selective desulfenylation of indole 2,3-bis(sulfides).[8] Sulfenylation of 2-indolyl sulfides occurs as expected at the 3-position, selectively affording mixed indole 2,3-bis(sulfides) in good yields. We were thus able to synthesize a series of complementary mixed bis(sulfides) (Table 1) to be used in the mechanistic study of the second sulfenylation of indole.

For the mechanistic study, we selected "matched sets" of examples where the groups attached to sulfur had significantly different electronic properties. For example, the sulfenylation of 3-(phenylthio)indole with methanesulfenyl chloride was compared with the complementary sulfenylation of 3-(methylthio)indole with benzenesulfenyl chloride. In the event that the process should involve transient generation of a 3,3-disubstituted species such as in eq 2, both reactions might be expected to afford similar ratios of the two mixed 2,3-bis(sulfides), resulting from a common intermediate. Similar competitive studies with other substituents would be expected to afford clues as to the relative migratory properties of the groups involved in relation to their electronic character.

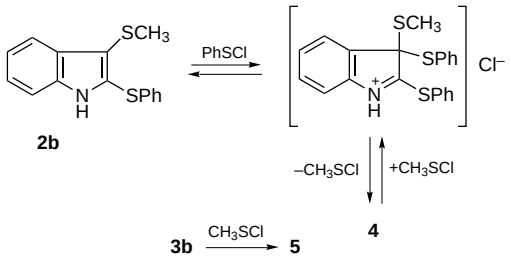
The experiments were performed as follows: a solution of the desired sulfenyl chloride (0.5 M) was prepared by adding sulfuryl chloride (SO_2Cl_2) to a solution of the appropriate disulfide in 1,2-dichloroethane.[3] Then 0.525 mmol of this solution was added to a solution of a chosen 3-indolyl sulfide (0.5 mmol) in DMF. The reaction was allowed to run at room temperature for 45 min and then worked up as described in the Experimental Section. The crude reaction mixtures were assayed by a combination of TLC and HPLC analyses, and, in some cases, crude chromatography was necessary to separate the mixture into two fractions containing components which had similar retention times by HPLC but different R_f's on silica gel, allowing quantitation by HPLC analysis of the two separate fractions. Quantitation was effected by comparison of peak areas with calibration curves obtained using several concentrations of the different standards. As will be seen, the study was complicated by several side reactions affording multi component mixtures. We quantified only components which were present at concentrations greater than 5% of the total mixtures. Each experiment was repeated twice, and the results reported correspond to the average value observed for each component.

(6) Plate, R.; Ottenheijm, H. C. J. *Tetrahedron* **1986**, *42*, 4511.
(7) Hamel, P.; Girard, Y.; Atkinson, J. G. *J. Org. Chem.* **1992**, *57*, 2694.
(8) Hamel, P.; Zajac, N.; Atkinson, J. G.; Girard, Y. *J. Org. Chem.* **1994,** *59*, 6372.

Scheme 1



Scheme 2

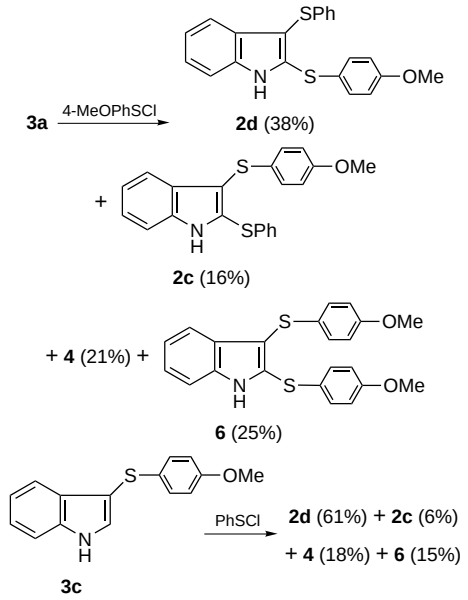


Results

Study Number 1: Methyl vs Phenyl (Scheme 1). When 3-(phenylthio)indole (**3a**) was sulfenylated with a slight excess of methanesulfenyl chloride as described above, the results, as shown in Scheme 1, were quite surprising: along with a 35% recovery of **3a**, the mixture consisted of 2% of **2a** and 47% of **2b**, corresponding to a **2b/2a** ratio of 23.5:1 in favor of the isomer in which the phenylthio group present at the 3-position of the starting material **3a** has migrated to the 2-position. However, the symmetrical 2,3-bis(phenylthio)indole (**4**) was present (12%), as well as 2,3-bis (methylthio)indole (**5**) (4%).

The complementary sulfenylation of 3-(methylthio)-indole (**3b**) with benzenesulfenyl chloride also afforded a complex mixture of components. In this case **2a** and **2b** were obtained in 10 and 38% yields, respectively, along with 9% of residual **3b**, as well as the two symmetrical bis(sulfides) **4** (25%) and **5** (18%). Although the formation of the symmetrical bis(sulfides) may seem surprising at first, they may be explained easily as follows: the bis(sulfide) **2b** may itself be subjected to sulfenylation (Scheme 2), affording a 2,3,3-trisubstituted transient species in which either of the two 3-substituents

Scheme 3



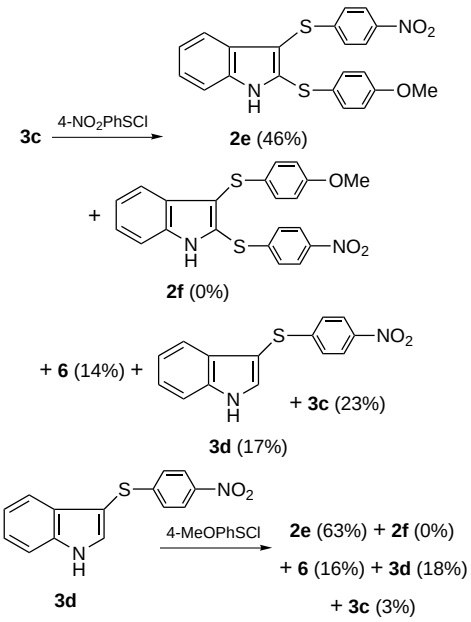
can be ejected, leading to **4** and/or **2b**; if the CH_3S group is ejected, putatively as CH_3SCl, it can react with the starting material **3b** to afford 2,3-bis(methylthio)indole (**5**). In a control experiment when **2b** was subjected to benzenesulfenyl chloride, extensive transformation to **4** was confirmed by TLC and HPLC. This experiment suggests that the **4** which is obtained in the original mixture could result from initial formation of **2b**, thus greatly increasing the "formal" proportion of **2b/2a** resulting from the initial sulfenylation. Thus in both experiments, the major mixed bis(sulfide) observed is the one in which the phenylthio group is present at the 2-position.

Study Number 2: Phenyl vs 4-Methoxyphenyl (Scheme 3). The results of sulfenylation of 3-(phenylthio)indole (**3a**) with 4-methoxybenzenesulfenyl chloride were as follows: **2c** (16%) and **2d** (38%) were obtained along with significant amounts of the symmetrical bis(sulfides) **4** (21%) and **6** (25%). The same reasoning as in the previous experiments can be used to explain the formation of these two components, and a control experiment confirmed the displacement of the 3-phenylthio group from **2d** by 4-methoxybenzenesulfenyl chloride.

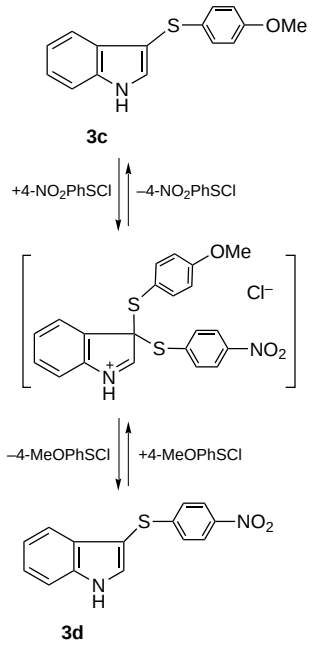
The results from the complementary sulfenylation of 3-((4-methoxyphenyl)thio)indole (**3c**) with benzenesulfenyl chloride also showed a preponderance of **2d** (61%) over **2c** (6%), along with the two symmetrical bis(sulfides) **4** (18%) and **6** (15%). In both studies, the major mixed bis(sulfide) observed has the (4-methoxyphenyl)thio group at the 2-position.

Study Number 3: 4-Methoxyphenyl vs 4-Nitrophenyl (Scheme 4). In this study we compared an electron-rich substituent with one which is strongly electron-deficient. Reaction of 3-((4-methoxyphenyl)thio)indole (**3c**) with 4-nitrobenzenesulfenyl chloride led to puzzling results: along with unreacted **3c** (23%) there was obtained **2e** (46%), 2,3-bis((4-methoxyphenyl)thio)indole **6** (14%), and 3-((4-nitrophenyl)thio)indole (**3d**) (17%)! No trace of **2f** was detected. Our explanation for the formation of **3d** is outlined in Scheme 5: Initial attack of the sulfenyl chloride leads to the 3,3-disubstituted indolenine intermediate. At this point, only partial migration occurs to afford **2e**, while a competing elimination of 4-methoxybenzenesulfenyl chloride leads to **3d**. The nascent sulfenyl chloride can react in several ways: with the starting material **3c**, to afford **6**; with **3d** leading to the results observed in the complementary experiment described below; also it can react with **2e**, in a displacement reaction similar to Scheme 3, to also afford **6**. This last process was confirmed by a control reaction. It is not surprising that, although **3d** is produced in the mixture, it does not suffer a second sulfenylation to afford bis((4-nitrophenyl)thio)indole (**7**), since more vigorous conditions are required to produce this second substitution (cf. preparation of **7** in Experimental Section).

Scheme 4



Scheme 5



The identification of **3d** in this experiment raises the question as to the possibility that a process such as outlined in Scheme 5 could have occurred in the previous experiments. Indeed, minor peaks corresponding to the complementary 3-indolyl sulfides were detected in the HPLC tracings of all of the mixtures studied, suggesting that such a displacement may have occurred.

As a complementary experiment, 3-((4-nitrophenyl)-thio)indole (**3d**) was allowed to react with 4-methoxybenzenesulfenyl chloride, leading to the following mixture: unreacted **3d** (18%), **2e** (63%), **6** (16%), and **3c** (3%). Once again, **2f** was not detected in any significant quantity.

Although the results of these last two experiments were complicated by several side reactions, it is significant that the *only* mixed bis(sulfide) observed was **2e**, having the (4-methoxyphenyl)thio group at the 2-position, in both experiments, with no trace of the isomeric **2f**.

Discussion

From careful examination of the mechanism outlined in eq 2, it should be possible to predict which of the two sulfide groups would be most likely to migrate to the 2-position. Since this migration is promoted by the positive charge on the indole nitrogen, it is reasonable to suggest that the sulfur bearing the substituent with the highest electron density would have a greater propensity to migrate. The results of the above series of experiments appear to support this hypothesis, as in each case the major mixed bis(sulfide) formed is the one in which the sulfide bearing the most electron-donating substituent occupies the 2-position of the indole ring.

Although an array of side reactions made analysis of the reaction mixtures more tedious than was expected, it is important to point out that all of these reactions appear to be due to attack at the 3-position already bearing a sulfide group. This observation supports the premise that this position remains the most reactive on the ring and greatly enhances the probability that the mechanism outlined in eq 2 is, at the very least, predominant. In fact, a process such as described in Scheme 2, which represents a *third* sulfenylation, should have been *expected* to happen, on the basis of our working hypothesis.

The complexity of the reaction mixtures suggests that variations in the relative proportions of the reagents, as well as in the reaction times, should lead to mixtures where the relative proportions of components would differ from those that we have obtained. However, we feel that it is reasonable to assume that similar trends would be observed and that the results would lead to the same conclusions.

Conclusion

We have developed an efficient, facile regioselective synthesis of mixed indole 2,3-bis(sulfides). The availability of these compounds allowed us to perform a study of the mechanism of the second sulfenylation of indole, which demonstrates that this process occurs predominantly, if not completely, by initial substitution at the 3-position of the ring, leading to a 3,3-disubstituted indolenine intermediate, followed by migration of one of the sulfide groups to the 2-position, as has been suggested by Ottenheijm.[4] The mechanism of this migration, proposed to occur in an intramolecular fashion via a transient episulfonium species, remains to be demonstrated. Although our data may be considered to be compatible with this hypothesis, we cannot rule out at this time the possibility of a more complex, intermolecular process.

Experimental Section

All reactions were carried out under N_2 atmosphere, although this may not be necessary. Reagents and solvents from commercial sources were used without further purification or drying. Melting points were recorded in open capillary tubes and are uncorrected. Infrared spectra were recorded using KBr pellets, and the values reported correspond to the largest or the most characteristic absorptions. The 300 MHz proton NMR data were collected using a Bruker instrument. Elemental analyses were provided by Guelph Chemical Laboratories Ltd., Guelph, Ontario.

Starting Materials: 3-Indolyl Sulfides. All of the 3-indolyl sulfides used in this study have been previously reported.[2,7]

2-Indolyl Sulfides. All of the 2-indolyl sulfides used in the preparation of the mixed bis(sulfides) have been reported[7] except 1f.

2-((4-Nitrophenyl)thio)indole (**1f**) was obtained by trifluoroacetic acid (TFA)- catalyzed isomerization[7] of 3-((4-nitrophenyl)thio)indole (**3d**): 253 mg of the 3-indolyl sulfide (1 mmol) and 8 mL of TFA were refluxed for 1.5 h. After cooling, the TFA was evaporated. The residue was dissolved in ether, and the solution was washed several times with water, dried over $MgSO_4$, and evaporated down to a mixture which was chromatographed on silica gel, eluting with 10% EtOAc in toluene to afford, as the least polar component, 152 mg of **1f** as a yellow solid (60%), mp 104−106 °C. IR: 3420-(NH), 1570, 1505 and 1330 (NO_2) cm^{-1}. ^1H NMR (acetone-d_6): δ 6.98 (s, 1H), 7.13 (m, 1H), 7.26 (m, lH), 7.30 (d, $J = 9.1$ Hz, 2H), 7.47 (d, $J = 8.3$ Hz, 1H), 7.67 (d, $J = 8$ Hz, 1H), 8.15 (d, $J = 9.1$ Hz, 2H), 10.8 (NH).

Anal. Calcd for $C_{14}H_{10}N_2O_2S$: C, 62.21; H, 3.73; N, 10.36; S, 11.86. Found: C, 62.36; H, 3.76; N, 10.47; S, 12.15. There was also obtained, as a more polar component, 68 mg of the bis(sulfide) **7** (see below for preparation).

Symmetrical Indole 2,3-Bis(sulfides). The bis sulfides **4**, **5** and **6** have been previously reported.[8]

2,3-Bis((4-nitrophenyl)thio)indole (**7**). To a suspension of 2.31 g of 4-nitrophenyl disulfide (7.5 mmol) in 20 mL of 1,2-dichloroethane there was added 0.57 mL of sulfuryl chloride (945 mg, 7 mmol), and the resulting mixture was refluxed for 30 min. After cooling, the dark yellow solution was added slowly at rt to a solution of 585 mg of indole (5 mmol) in 10 mL of DMF. The resulting mixture was refluxed for 30 min. After cooling, the dichloroethane was evaporated away. The residual DMF solution was diluted with water and extracted twice with ether. These extracts were washed twice with water, dried, and evaporated to a residue which was chromatographed on silica gel, eluting with a 1:5 mixture of EtOAc and hexane to afford 1.09 g of **7** as a yellow solid, mp 163−165 °C. IR: 3380 (NH), 1575, 1510 and 1335 (NO_2) cm^{-1}. ^1H NMR (acetone-d_6): δ 7.24 (d, $J = 9$ Hz, 2H), 7.25 (m, 1H), 7.38 (d, $J = 9$ Hz, 2H), 7.40 (m, 1H), 7.56 (d, $J = 8$ Hz, 1H), 7.63 (d, $J = 8.3$ Hz, 1H), 8.03 (d, $J = 9$ Hz, 2H), 8.10 (d, $J = 9$ Hz, 2H). The NH proton was not observed.

General Procedures for the Synthesis of Mixed Indole 2,3-Bis(sulfides). Method A:[3]2-(Methylthio)-3-(phenylthio)indole (2a). To a solution of 196 mg of diphenyl disulfide (0.9 mmol) in 2 mL of 1,2-dichloroethane at room temperature there was added 61 μL of sulfuryl chloride (101 mg, 0.75 mmol). The resulting yellow solution, after being stirred for 5 min, was added to a solution of 196 mg of 2-(methylthio)-indole (**1a**) (1.2 mmol) in 2 mL of DMF. The resulting mixture was stirred for 1 h, the reaction was quenched with water, and the solution was extracted three times with ether. The organic phase was washed twice with water, dried over $MgSO_4$, filtered, and evaporated to a residue which was chromatographed on silica gel, eluting with a 1:5 mixture of ethyl acetate and hexane. There was obtained 289 mg of **2a** (89%) as a beige solid, mp 87−89 °C. IR: 3442, 1475, 1435, 743 cm^{-1}. ^1H NMR ($CDCl_3$): δ 2.47 (s, 3H), 7.05−7.25 (m, 7H), 7.38 (d, $J = 8.1$ Hz, 1H), 7.54 (dd, $J = 0.8$ and 7.7 Hz, 1H), 8.48 (br, NH). Anal. Calcd for $C_{15}H_{13}NS_2$: C, 66.38; H, 4.83; N, 5.16; S, 23.63. Found: C, 66.15; H, 5.00; N, 5.00; S, 23.32.

Also prepared in the same manner were the following.

3-(Methylthio)-2-(phenylthio)indole (**2b**): beige solid, mp 49−51 °C. IR: 3380, 1475, 1440, 735 cm^{-1}. ^1H NMR ($CDCl_3$): δ 2.34 (s, 3H), 7.19−7.31 (m, 8H), 7.78 (dd, J = 1.5 and 8.5 Hz, 1H), 8.22 (br, NH). Anal. Calcd for $C_{15}H_{13}NS_2$: C, 66.38; H, 4.83; N, 5.16; S, 23.63. Found: C, 66.45; H, 4.93; N, 4.93; S, 23.24.

3-((4-Methoxyphenyl)thio)-2-(phenylthio)indole (**2c**): off-white solid, mp 107−110 °C. IR: 3380, 1478, 1230, 740 cm^{-1}. ^1H NMR ($CDCl_3$): δ 3.73 (s, CH_3), 6.71 (d, J = 8.8 Hz, 2H), 7.12−7.32 (m, 8H), 7.17 (d, J = 8.8 Hz, 2H), 7.62 (dd, J = 0.7 and 8.9 Hz, 1H), 8.30 (br, NH). Anal. Calcd for $C_{21}H_{17}NOS_2$: C, 69.39; H, 4.71: N, 3.85; S, 17.64. Found: C, 68.99, H, 4.97; N, 3.70; S, 17.96.

2-((4-Methoxyphenylthio)-3-phenylthio)indole (**2d**): cream-colored solid, mp 113−115 °C. IR: 3380, 1490, 1245, 735 cm^{-1}. ^1H NMR ($CDCl_3$): δ 3.80 (S, 3H), 6.84 (d, J = 8.8 Hz, 2H), 7.06−7.30 (m, 8H), 7.38 (d, J = 8.8 Hz, 2H), 7.54 (d, J = 7.8 Hz, 1H) 8.13 (br, NH). Anal. Calcd for $C_{21}H_{17}NOS_2$: C, 69.39: H, 4.71; N, 3.85: S, 17.64. Found: C, 68.99; H, 4.83; N, 3.73; S, 17.63.

2-((4-Methoxyphenyl)thio)-3-((4-nitrophenyl)thio)indole (**2e**). For the preparation of 4-nitrobenzenesulfenyl chloride, the mixture of disulfide and SO_2Cl_2 in 1,2-dichloroethane was refluxed for 30 min and then cooled down and used as such. The **2e** was obtained as an orange solid, mp 114−116 °C (EtOH). IR: 3380, 1575, 1510, 1330 cm^{-1}. ^1H NMR ($CDCl_3$) δ 3.78 (s, 3H), 6.83 (d, J = 8.8 Hz, 2H), 7.07 (d, J = 9.0 Hz, 2H), 7.13−7.36 (m, 3H), 7.39 (d, J = 8.8 Hz, 2H), 7.47 (d, J = 7.7 Hz, 1H), 7.98 (d, J = 9.0 Hz, 2H), 8.29 (br, NH). Anal. Calcd for $C_{21}H_{16}N_2O_3S_2$: C, 61.75; H, 3.95; N, 6.86; S, 15.70. Found: C, 61.68; H, 3.87; N, 6.92; S, 15.44.

3-((4-Methoxyphenyl)thio)-2-((4-nitrophenyl)thio)indole (**2f**): yellow crystals, mp 153−155 °C (EtOH). IR: 3375 (br), 1575, 1508, 1330 cm^{-1}. ^1H NMR ($CDCl_3$): δ 3.71 (s, 3H), 6.66 (d, J = 9 Hz, 2H), 7.06 (d, J = 9 Hz, 2H), 7.15 (d, J = 9 Hz, 2H), 7.21−7.44 (m, 3H), 7.73 (d, J = 7.9 Hz, 1H), 7.99 (d, J = 9 Hz, 2H), 8.50 (br, NH). Anal. Calcd for $C_{21}H_{16}N_2O_3S_2$: C, 61.75; H, 3.95; N, 6.86; S, 15.70. Found: C, 61.43; H, 3.81; N, 6.84; S, 15.78.

Method B[2]. **2-((4-Chlorophenyl)thio)-3-((4-methoxyphenyl)thio)indole** (**2g**). To a suspension of 16 mg of 97% NaH (0.67 mmol) in 1.5 mL of DMF there was added 130 mg of 2-((4-chlorophenyl)thio)indole (**1g**) (0.5 mmol), and the resulting mixture was stirred at room temperature under an N_2 atmosphere until gassing subsided (30 min). There was added 167 mg of 4-methoxyphenyl disulfide (0.6 mmol) and the mixture was stirred at room temperature overnight. The reaction was quenched with saturated aqueous NH_4Cl, and the solution was diluted with water and extracted twice with ether. The crude product from the organic phase was chromatographed on silica gel, eluting with a 1:5 mixture of EtOAc and hexane, to afford 160 mg of **2g** (80%) as an oil which solidified. Crystallization from ether−hexane gave cubic crystals, mp 99−101 °C. IR: 3265, 1490, 1470, 1250 cm^{-1}. ^1H NMR ($CDCl_3$): δ 3.73 (s, 3H), 6.69 (d, J = 8.8 Hz, 2H), 7.08−7.19 (m, 7H), 7.29 (m, 2H), 7.65 (d, J = 7.9 Hz, 1H) 8.32 (br, NH). Anal. Calcd for $C_{21}H_{16}ClNOS_2$: C, 63.38; H, 4.05; N, 3.52; S, 16.11; Cl, 8.91. Found: C, 63.50; H, 4.18; N, 3.47; S, 16.18; Cl, 9.21.

3-((4-Chlorophenyl)thio)-2-((4-methoxyphenyl)thio)indole (**2h**) was prepared in the same fashion from 2-((4-methoxyphenyl)thio)indole and 4-chlorophenyl disulfide: white rosettes, mp 92−94 °C (ether−hexane). IR: 3430, 1490, 1470, 1240, cm^{-1}. ^1H NMR ($CDCl_3$) δ 3.80 (s, 3H), 6.83 (d, J = 8.9 Hz, 2H), 6.98 (d, J = 8.6 Hz, 2H), 7.10 (d, J = 8.6 Hz, 2H), 7.08−7.30 (m, 3H), 7.37 (d, J = 8.9 Hz, 2H), 7.51 (d, J = 8.0 Hz, 1H), 8.16 (br, NH). Anal. Calcd for $C_{21}H_{16}ClNOS_2$: C, 63.38; H, 4.05; N, 3.52: S, 16.11; Cl, 8.91. Found: C, 63.59; H, 4.13; N, 3.48; S, 15.97; Cl, 9.26.

General Procedure for Sulfenylation of 3-Indolyl Sulfides with Sulfenyl Chlorides. Sulfenylation of 3-((4-nitrophenyl)thio)indole (3d) with 4-methoxybenzenesulfenyl Chloride. To a solution of 167 mg of 4-methoxyphenyl disulfide (0.6 mmol) in 2 mL of 1,2-dichloroethane there was added 41 μL of sulfuryl chloride (0.5 mmol). The resulting yellow orange solution was stirred at room temperature for 10 min, assuming formation of a 0.5 M solution of the sulfenyl chloride. From this solution, 1.05 mL (0.525 mmol) was added to a solution of 135 mg of **3d** (0.5 mmol) in 1 mL of DMF. The mixture was stirred at room temperature for 45 min, the reaction was quenched with water, and the solution was extracted twice with EtOAc. The organic phase was washed three times with water, dried over $MgSO_4$, and evaporated down to a residue which was analyzed by HPLC.

General Procedure for the Analysis of Sulfenylation Mixtures by HPLC. Mixtures were analyzed using a C_{18} reverse-phase column. The eluent in all cases was a 60:40 mixture of acetonitrile and deionized water, at a flow rate of 1 mL/min. UV detector wavelength was set at 254 nm. Stock solutions of the various standards were made up in CH_3CN, at four different concentrations, and calibration curves were obtained relating peak areas to concentrations.

Crude sulfenylation mixtures, all from 0.5 mM scale reactions, were dissolved in 250 mL of CH_3CN, and this solution was again dissolved by a factor of 50, affording an "assumed" 40 mM mixture. From this, 25 μL was injected onto the column. Retention times and peak areas were correlated with the appropriate compounds and concentrations, allowing the quantitation of each component. Results in the schemes represent the relative proportions of major constituents of the mixtures.

In study no. 2, the retention times of **2d** and **4** were the same; this was also the case for **2c** and **6**. However, these pairs of compounds had different R_f's on TLC. In both experiments, the crude sulfenylation mixture was initially chromatographed on three preparative TLC plates, eluting twice with a 1:5 mixture of EtOAc and hexane. The plate area was separated in two, and the silica was extracted separately with EtOAc, affording two mixtures, one containing **2d** and **6**, the other containing **2c** and **4**. The two mixtures were analyzed separately, allowing quantitation of the compounds which had similar retention times in the original mixture.

Control Experiments: Reaction of 2b with Benzenesulfenyl Chloride. Benzenesulfenyl chloride was prepared as described above from Ph_2S_2 and SO_2Cl_2 in 1,2-dichloroethane. A volume equivalent to 0.12 mmol was added to a solution of 27 mg of **2b** (0.1 mmol) in 0.3 mL of DMF. The mixture was stirred at r.t. A TLC taken after 5 min showed extensive transformation to **4**; the mixture was worked up after 30 min, and HPLC analysis showed a **4/2b** ratio of 5:1.

Reaction of 2d with 4-Methoxybenzenesulfenyl Chloride. A similar reaction on **2d**, reacting with 4-methoxybenzenesulfenyl chloride, worked up after 45 min, afforded a **6/2d** ratio of ca. 2:1.

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